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G1G GPB G6A

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EP 0829225 A2 EP 0829224 A2 EP 0282234 A1
Medical & Biological Engineering & Computing, Vol.
31(3), pp. 284-290, May 1993 Physics in medicine and
biology, Vol. 38(12), pp. 1911-1922, Dec 1993

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UK CL (Edition P) G1G GPB
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33/49
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(54) Abstract Title

In-vivo photoacoustic measurement

(57) A biological parameter is measured by directing laser pulses from a light guide (10) into a body part consisting of soft tissue, such as the tip of a finger (12), to produce a photo-acoustic interaction. Sound waves (14) generated by absorption of the optical beam are detected by a transducer (16). The detector and optical beam guide are housed in a body-part shaped sensor head device (figures 2 to 16), and are preferably not co-linear with one another. Analysis of the transducer output enables calculation of the desired parameter, e.g. blood glucose concentration.

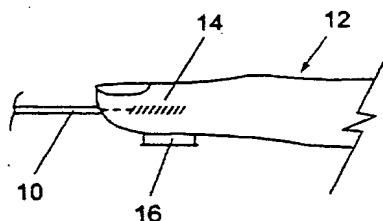


Fig. 1a

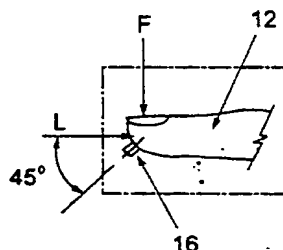


Fig. 1b

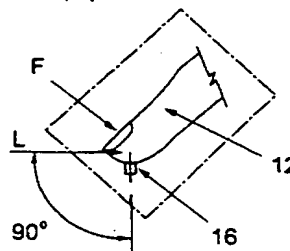


Fig. 1c

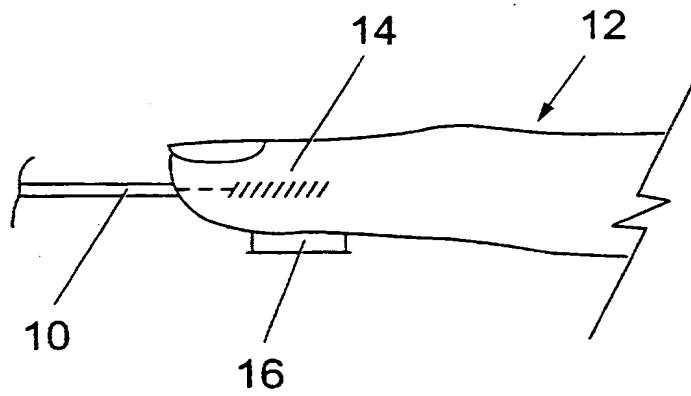


Fig. 1a

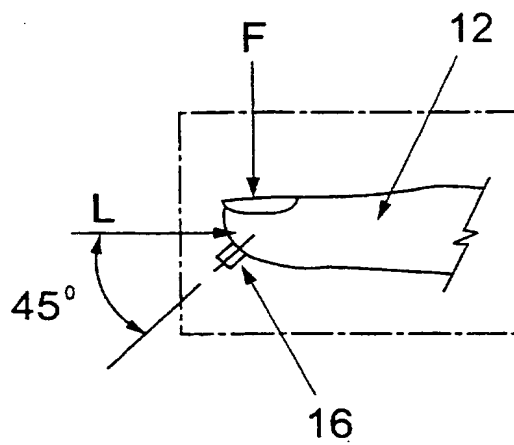


Fig. 1b

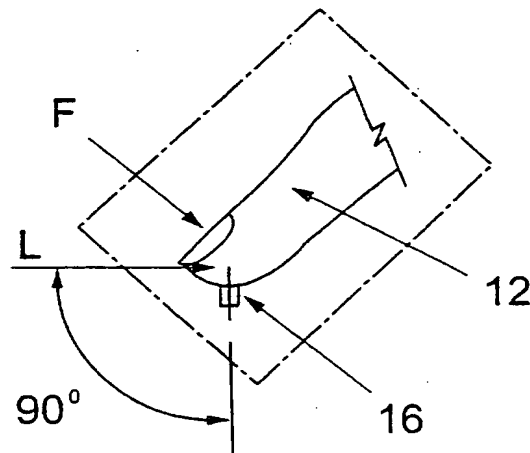


Fig. 1c

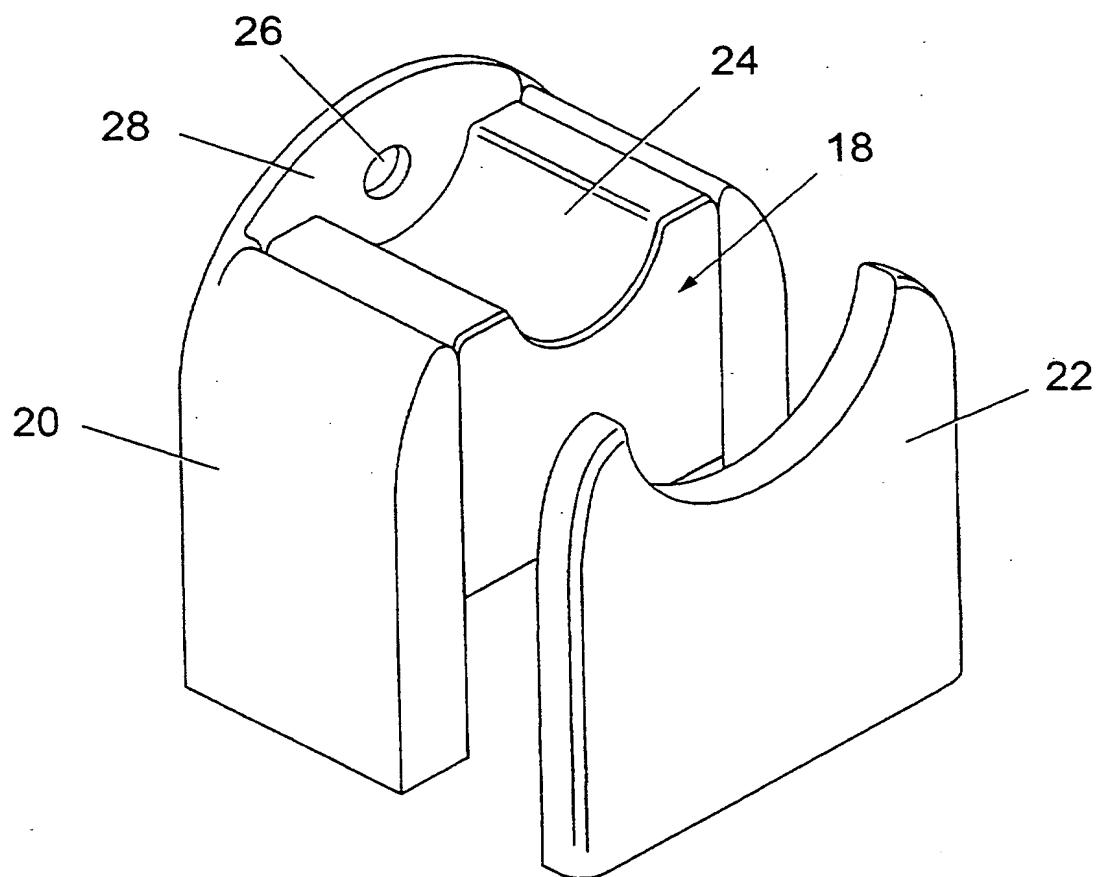


Fig. 2

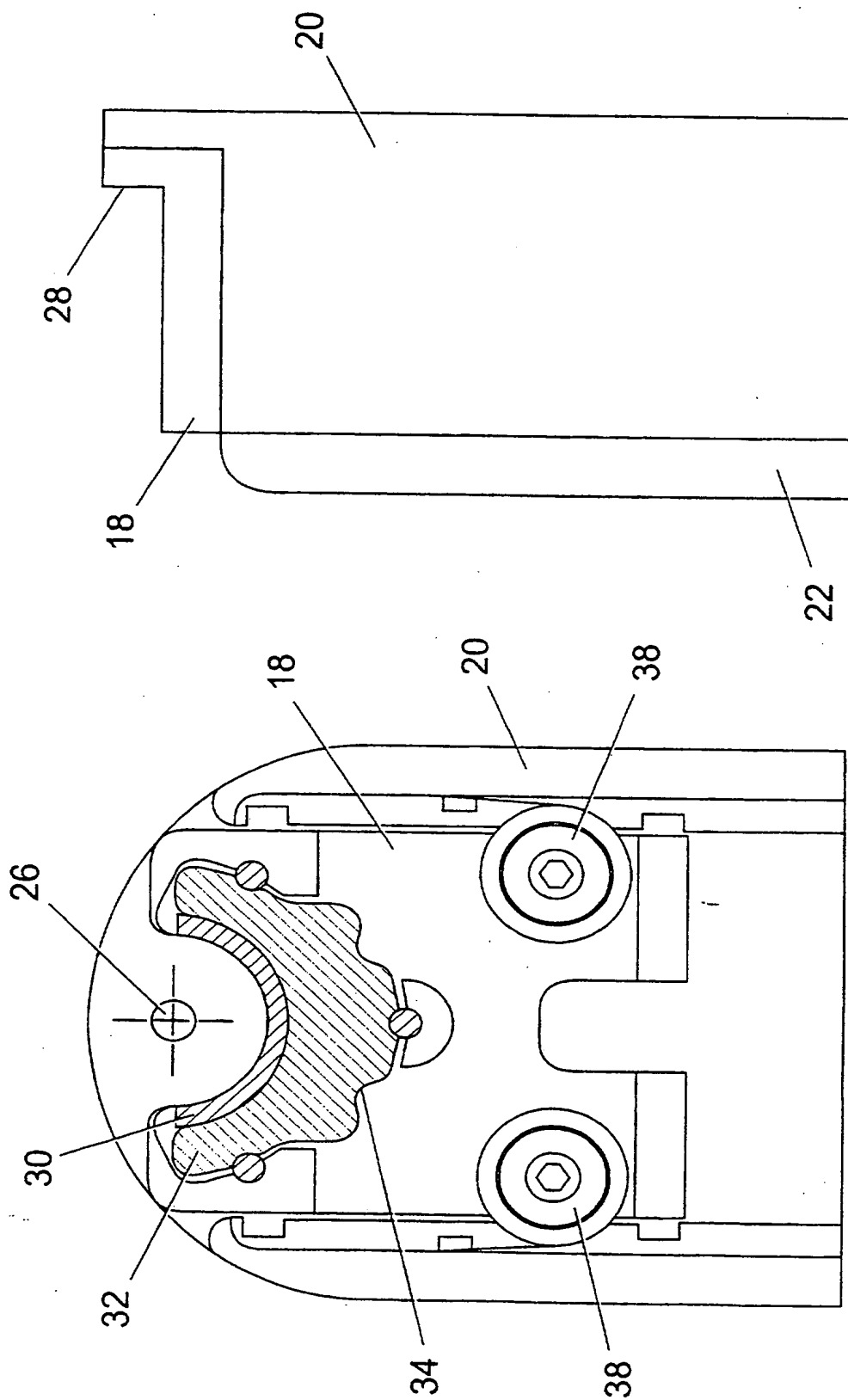


Fig. 4

Fig. 3

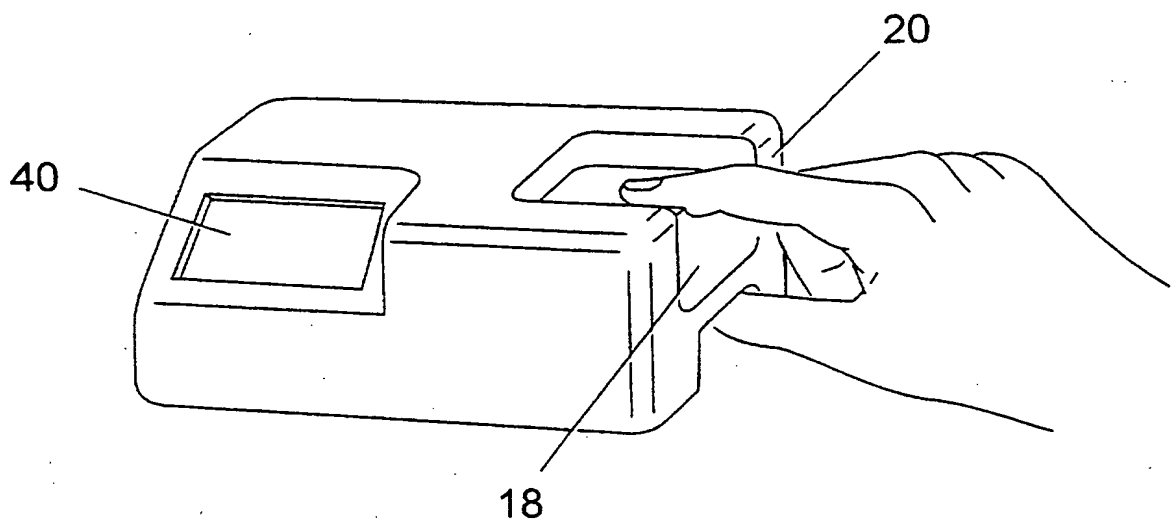


Fig. 5

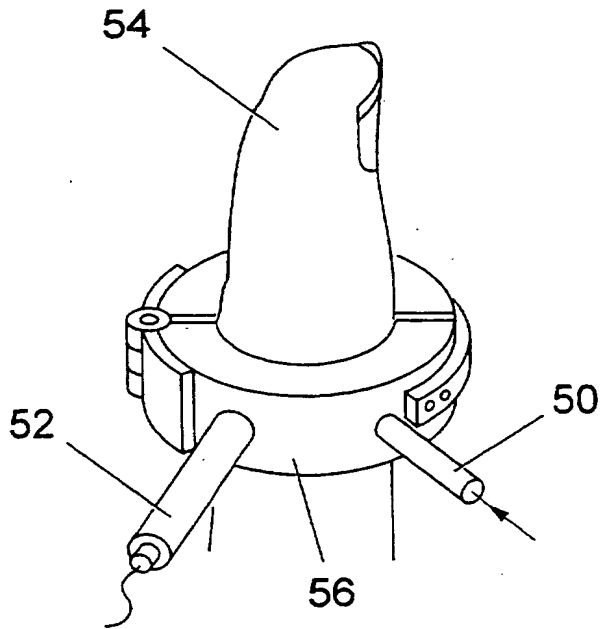


Fig. 6

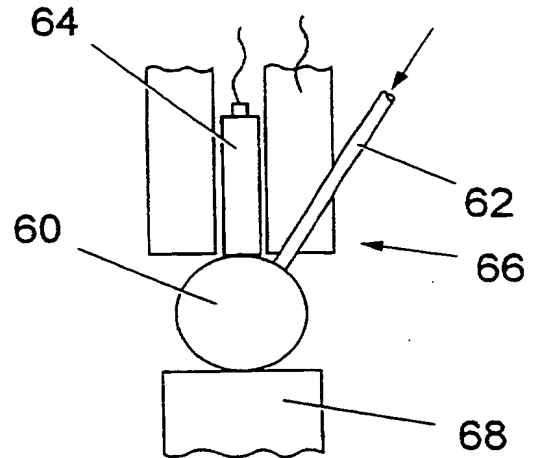


Fig. 7

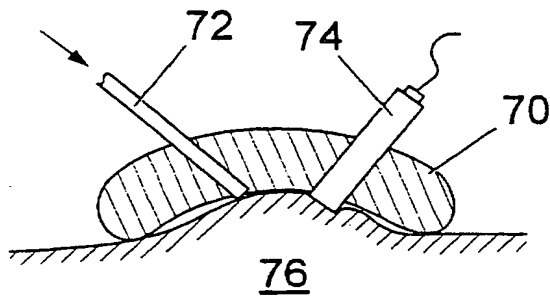


Fig. 8a

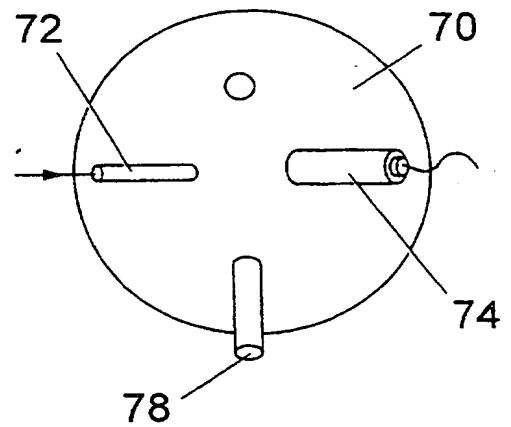


Fig. 8b

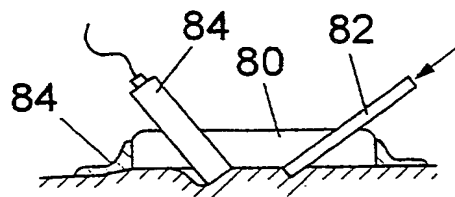


Fig. 9

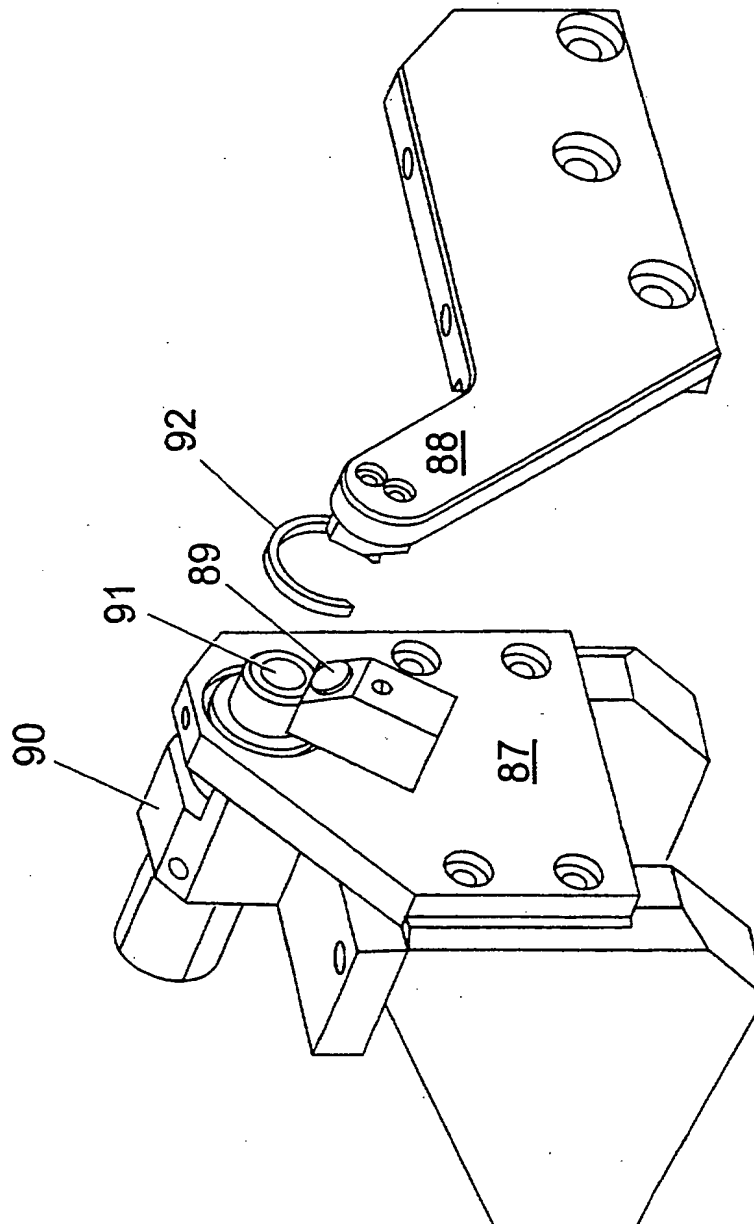
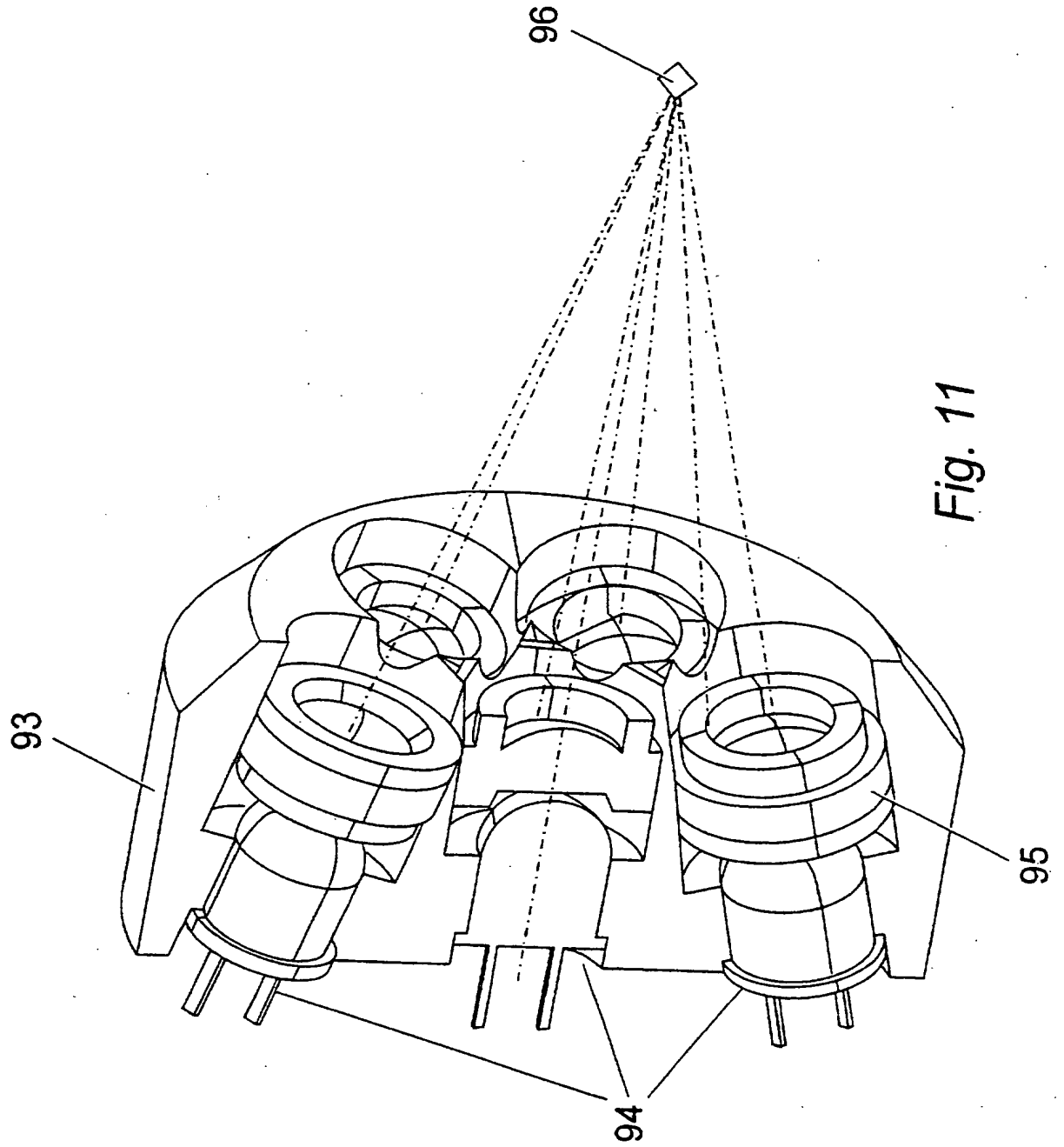


Fig. 10



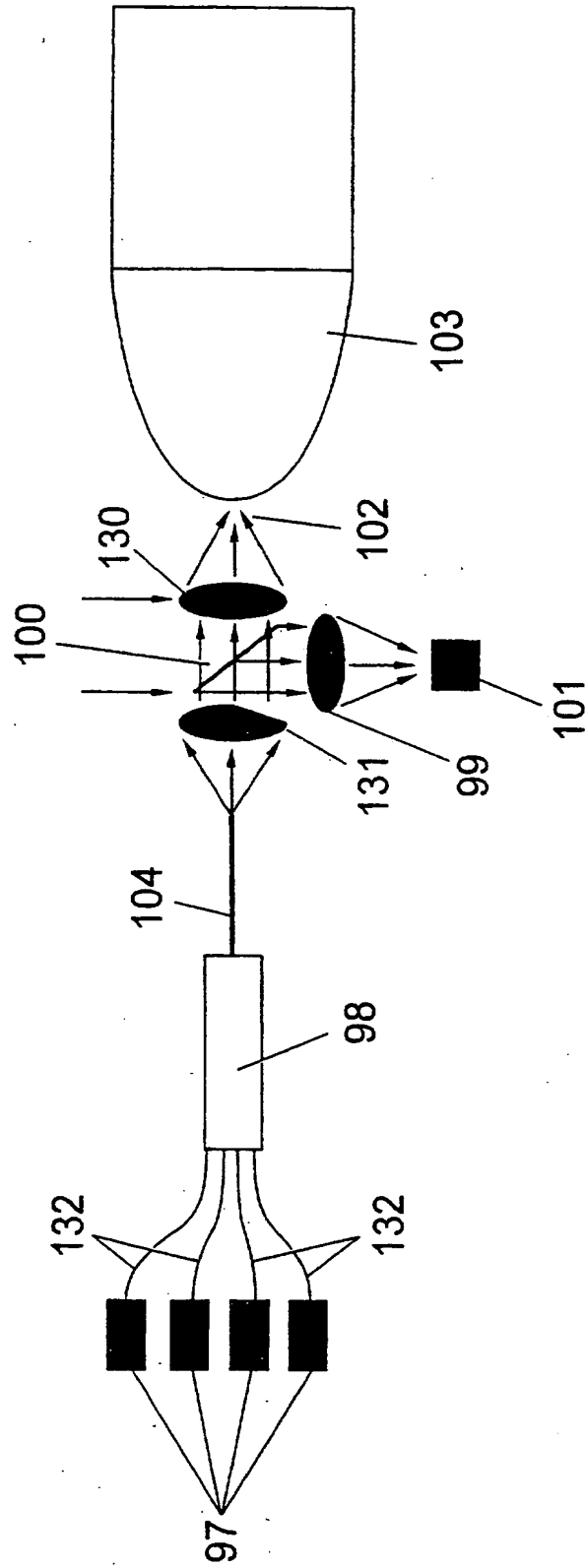


Fig. 12

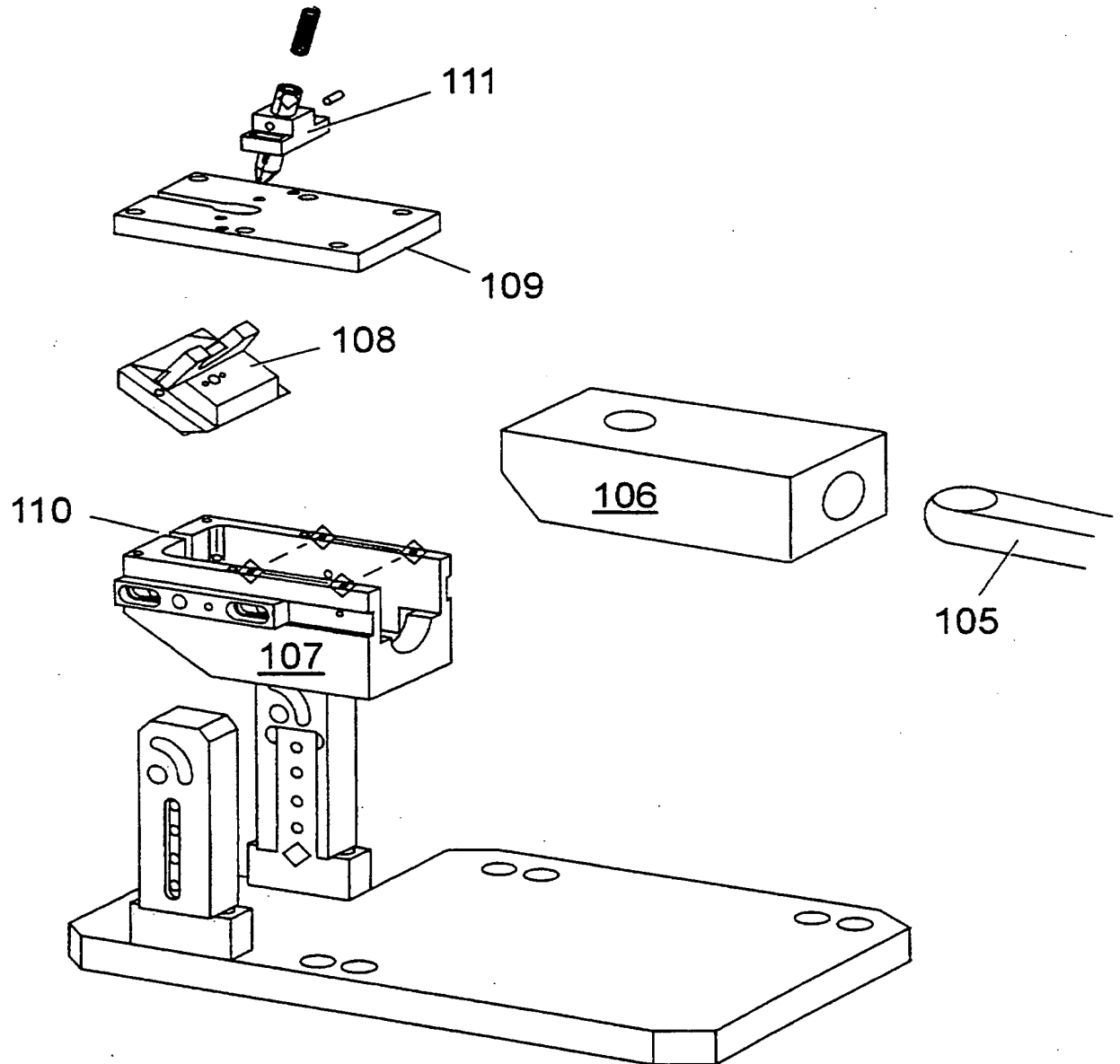


Fig. 13

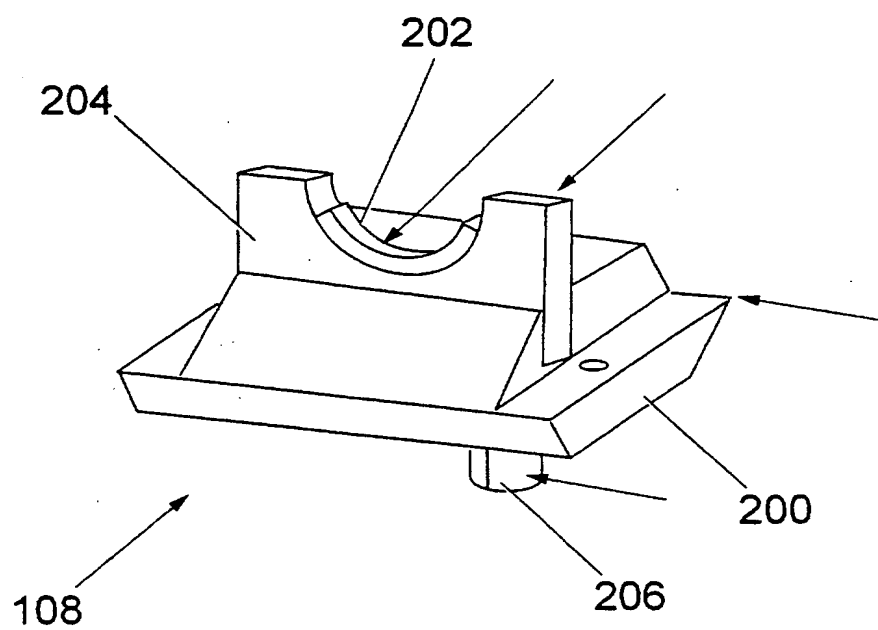


Fig. 13a

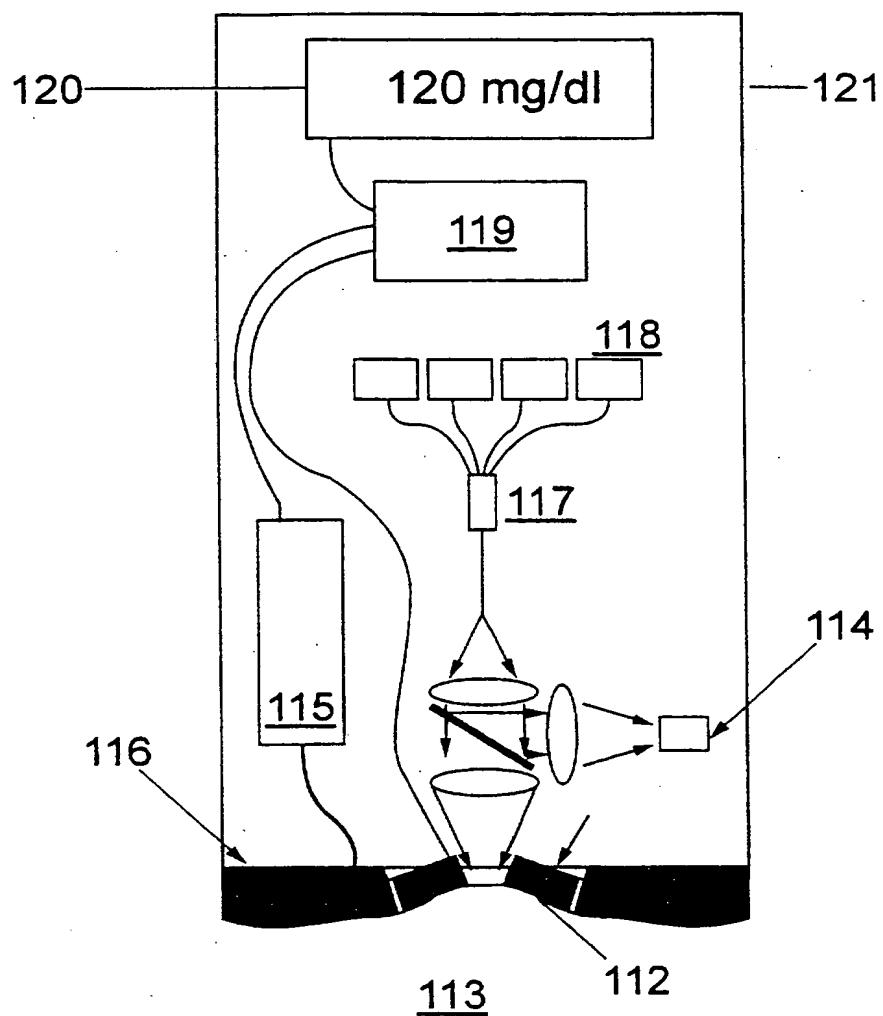


Fig. 14

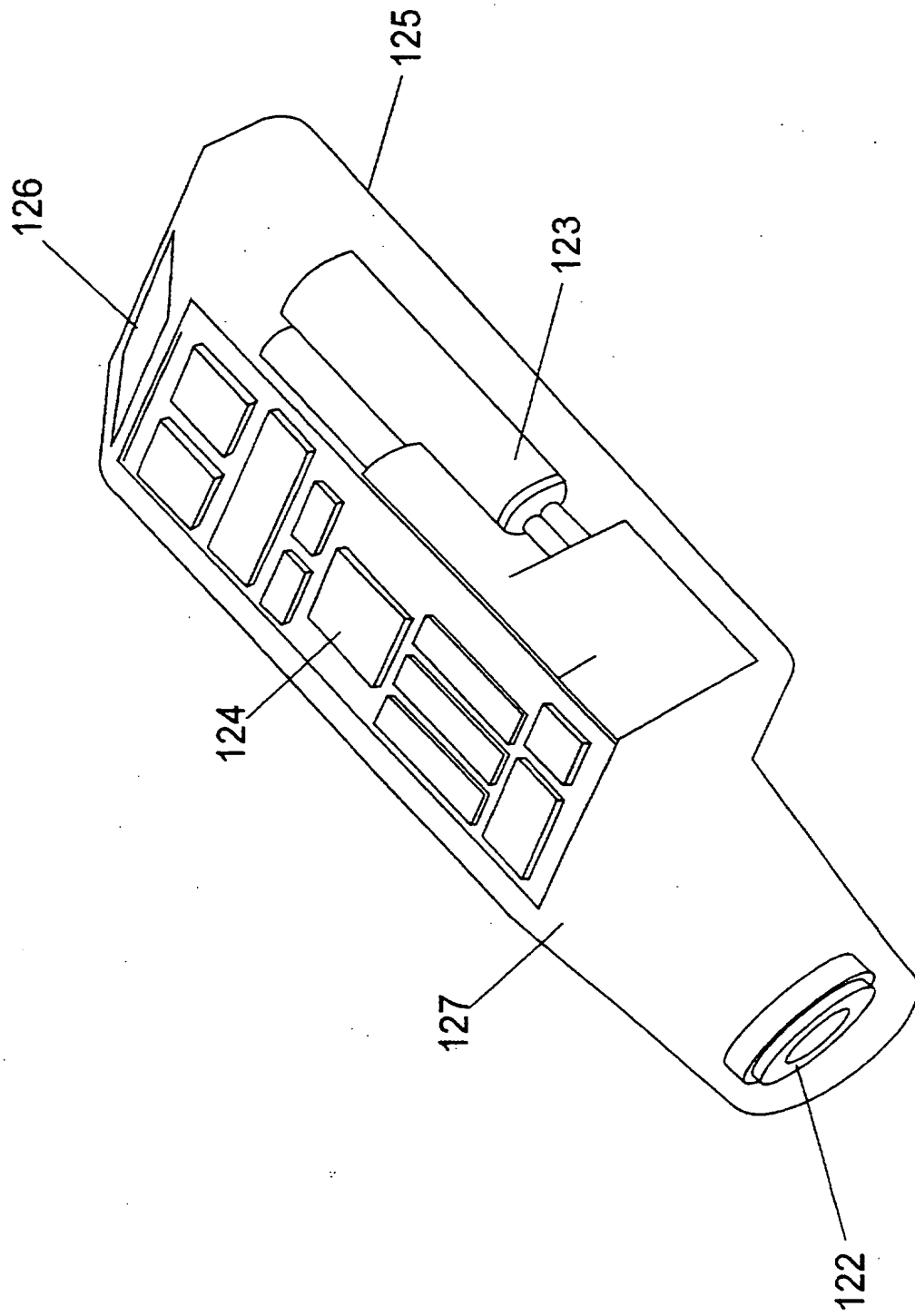


Fig. 15

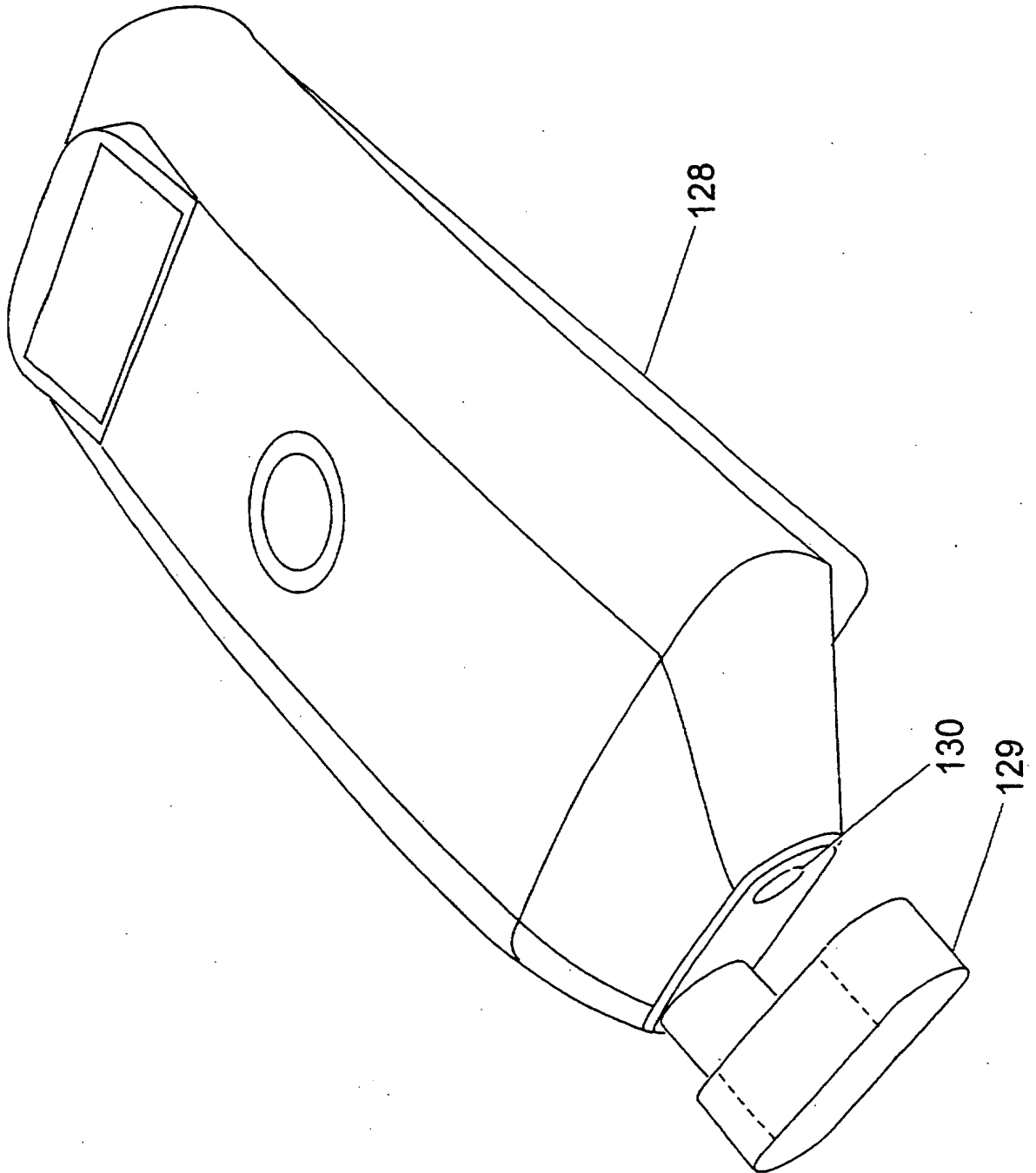


Fig. 16

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR NORMAL SUBJECT

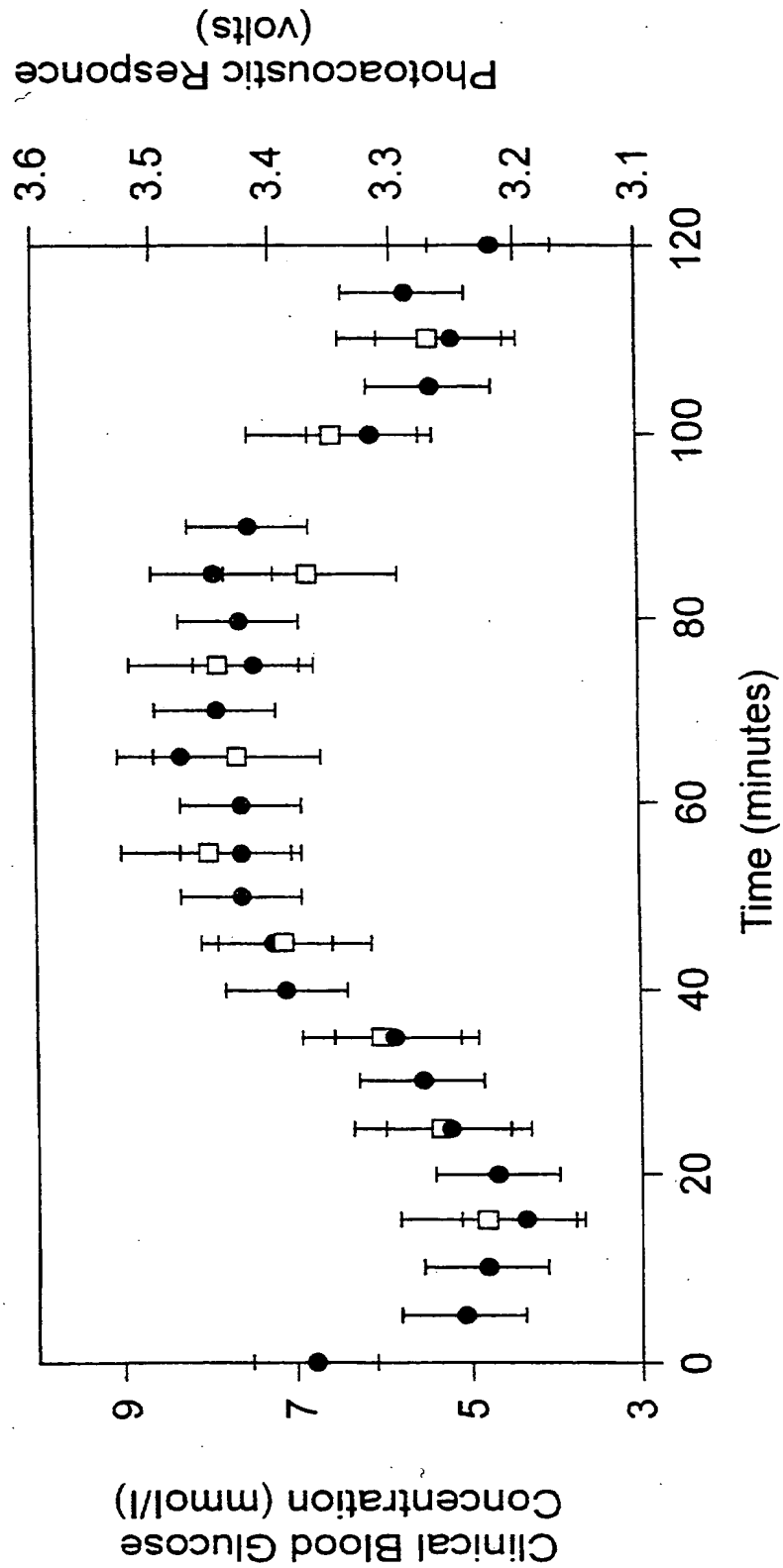


Fig. 17

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR TYPE 1 DIABETIC

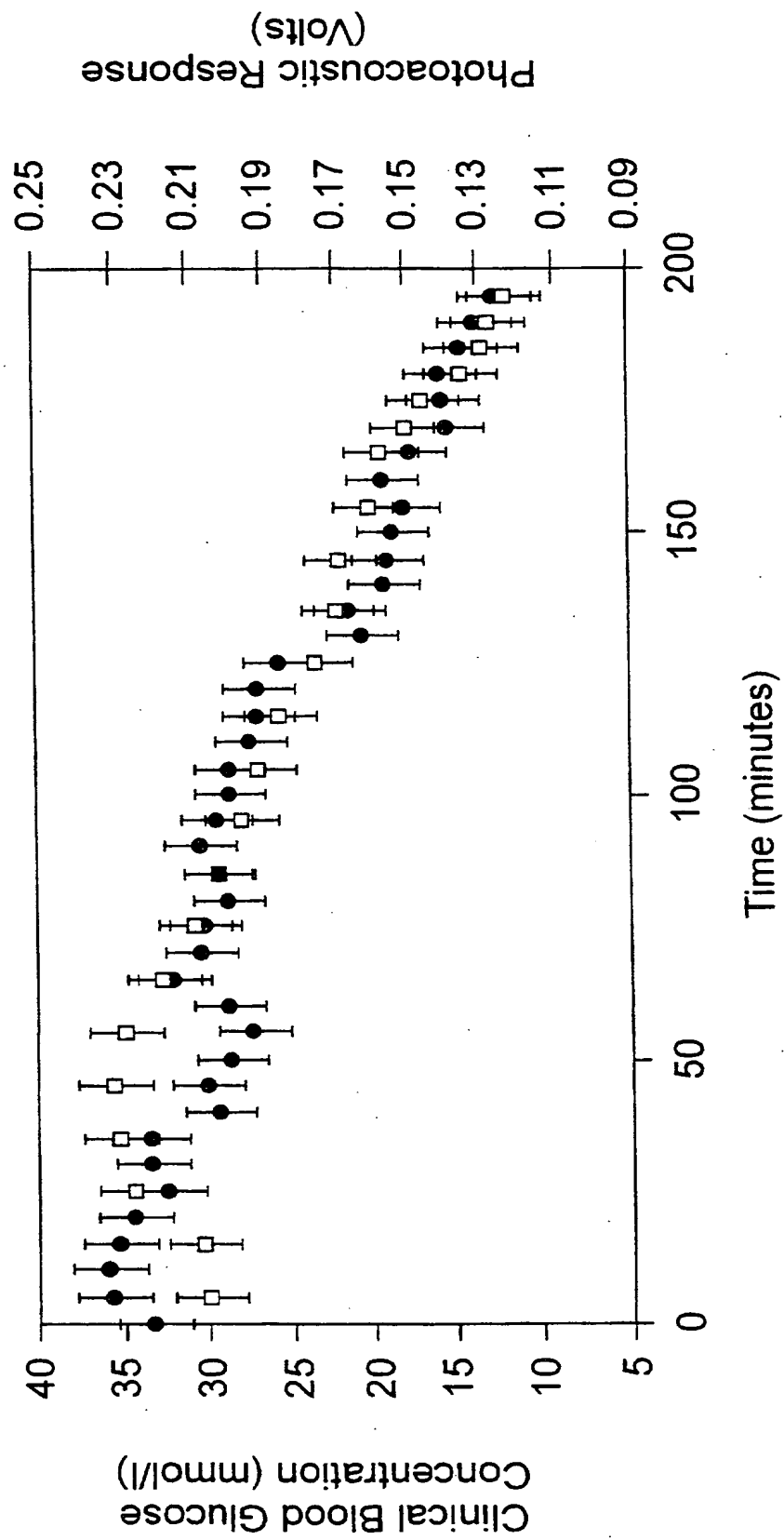


Fig. 18

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR TYPE 2 DIABETIC

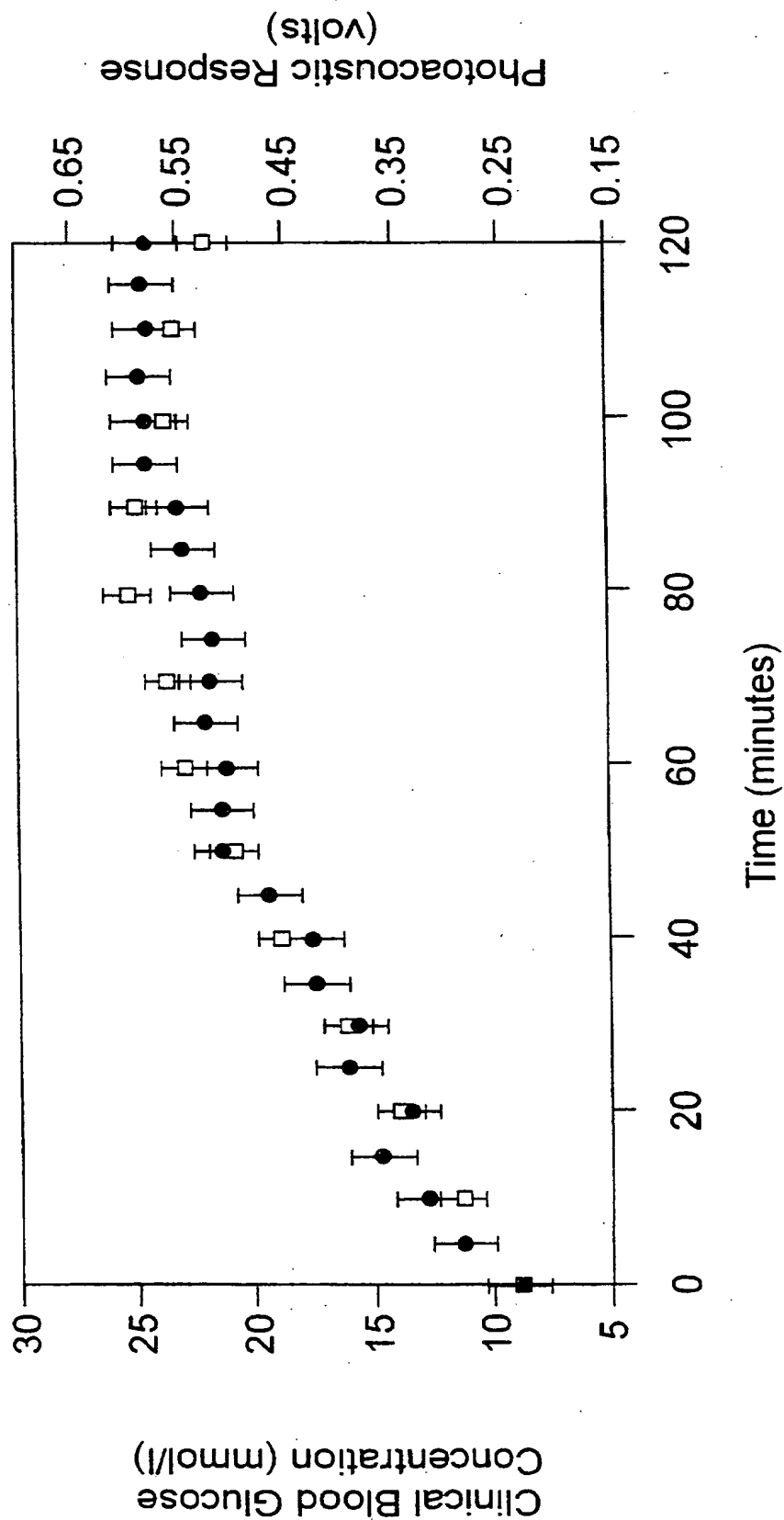


Fig. 19



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1

1 Biological Measurement System

2

3 This invention relates to apparatus for use in non-
4 invasive in vivo monitoring of physiological substances
5 such as blood and the like.

6

7 One particular, but not exclusive, application of the
8 present invention is in the monitoring of blood
9 glucose, for example in the management of diabetes
10 mellitus. It is accepted that the management of
11 diabetes can be much improved by routine monitoring of
12 blood glucose concentration and clinicians suggest that
13 monitoring as often as four times per day is desirable.

14

15 The monitoring technique currently available for use by
16 patients involves using a spring loaded lancet to stab
17 the finger to obtain a blood sample which is
18 transferred to a glucose test strip. The concentration
19 is derived either by reading the test strip with a
20 reflectance meter or by visual comparison of colour
21 change against a colour scale. Many diabetics find the
22 testing onerous as the technique is painful,
23 inconvenient, messy, potentially embarrassing and
24 offers a site for the transmittance and acceptance of
25 infection.

1 Techniques have also been developed for non invasive
2 measurement using transmittance or reflectance
3 spectroscopy. However the required instruments are
4 expensive and it is difficult to obtain accurate and
5 repeatable measurements.

6
7 There are also known various types of in vivo chemical
8 sensors. These rely on implanting minimally invasive
9 sensors under the skin surface, but such sensors have
10 poor long term reproducibility and bio-compatibility
11 problems.

12
13 There is therefore a need for improved means for
14 routine monitoring of blood glucose in a manner which
15 is simple and straightforward to use.

16
17 The present invention makes use of photoacoustic
18 techniques. The fundamentals of photoacoustic
19 techniques are well known per se. A pulse of light,
20 typically laser light, is applied to a substance
21 containing an analyte of interest in solution or
22 dispersion, the wavelength of the applied light being
23 chosen to interact with the analyte. Absorption of the
24 light energy by the analyte gives rise to microscopic
25 localised heating which generates an acoustic wave
26 which can be detected by an acoustic sensor. These
27 techniques have been used to measure physiological
28 parameters in vitro.

29
30 US Patents 5348002 and 5348003 (Caro) propose the use
31 of photoacoustics in combination with photoabsorption
32 for the measurement of blood components in vivo.
33 However, the arrangement proposed by Caro has not been
34 demonstrated as a workable system and may suffer from
35 interference to a degree which would preclude useful
36 acoustic signals, and since they would also suffer from

1 interference and resonance effects from hard structures
2 such as bone.

3
4 It has also been proposed by Poulet and Chambron in
5 Medical and Biological Engineering and Computing,
6 November 1985, Page 585 to use a photoacoustic
7 spectrometer in a cell arrangement to measure
8 characteristics of cutaneous tissue, but the apparatus
9 described would not be suitable for measuring blood
10 analytes.

11
12 Published European Patent Application 0282234A1
13 (Dowling) proposes the use of photoacoustic
14 spectroscopy for the measurement of blood analytes such
15 as blood glucose. This disclosure however does not
16 show or suggest any means which would permit the
17 required degree of coupling to body tissues for use in
18 vivo.

19
20 Accordingly, the present invention provides a sensor
21 head for use in photoacoustic in vivo measurement,
22 comprising a housing shaped to engage a selected body
23 part, light transmission means terminating in said
24 housing so as to transmit light energy from a light
25 source to enter the body part along a beam axis, and
26 acoustic transducer means mounted in the housing to
27 receive acoustic waves generated by photoacoustic
28 interaction within the body part, the acoustic
29 transducer means being disposed in the housing to
30 receive said acoustic wave in a direction of high
31 acoustic energy.

32
33 The expression "direction of high acoustic energy" is
34 used herein to denote a direction other than the
35 forward direction of the light beam. Preferably, the
36 transducer means is disposed so as to intercept

1 acoustic energy propagating at right angles to the
2 optical beam axis, or at an angle to the optical beam
3 axis which may be down to about 20° , typically about
4 45° .

5
6 An exact measure of the angle of high acoustic energy
7 can be worked out but is dependent upon the specific
8 geometry of the light source, the properties of the
9 tissue and the absorption coefficient of the tissue.
10 One model for understanding the propagation of the
11 acoustic energy in any homogenous media was developed
12 by Huyghens and is called the principle of
13 superposition. In this model each volume element that
14 is illuminated by the light generates an acoustic
15 pressure wave that radiates outward in a spherical
16 manor. The magnitude of the pressure wave at each
17 volume element depends on the intensity of the optical
18 beam at that location, the absorption coefficient of
19 the material at that location, the wavelength of light
20 and on several other physical properties of the
21 material such as the speed of sound and the specific
22 heat. The signal measured at the detector is just the
23 superposition of all pressure waves from all points
24 that are illuminated by the source light. An
25 analytical solution for the pressure wave has been
26 worked out for a few cases in aqueous material. The
27 analytical case that best matches the in-vivo
28 measurements is that of a cylindrical optical beam
29 propagating in a weakly absorbing material. In this
30 case the direction of highest acoustic energy is
31 perpendicular to the optical axis. The base detector
32 location is with the plane of the detector
33 perpendicular to the acoustic energy, or parallel to
34 the optical axis. This is because the acoustic
35 detector has the highest sensitivity when the acoustic
36 energy strikes the detector perpendicular to the plane

1 of the detector. This analytical model is not
2 completely accurate for the in-vivo measurement case
3 because of scattering of the tissue and because the
4 tissue absorbs more than the model predicts. These
5 differences indicate that a different position for the
6 detector will be optimal. A detailed numeric model is
7 required to determine the best detector location and is
8 dependent upon the beam properties (focused to a point,
9 colligated, etc.), body site (finger, earlobe, arm
10 etc.) and wavelength. One skilled in the art can
11 readily develop an appropriate mode. However, suitable
12 locations for a detector will generally be at an angle
13 to the optical axis. Angles between 40 and 90 degrees
14 should be suitable.

15
16 In one preferred arrangement, the acoustic transducer
17 means is arranged parallel to the optical beam axis.
18 This arrangement is particularly suitable for use where
19 the selected body part is the distal portion of a
20 finger, in which case the housing may include a
21 generally half-cylindrical depression in which the
22 finger may be placed with the light transmission means
23 aimed at the end of the finger.

24
25 Preferably, the acoustic transducer means comprises a
26 piezoelectric transducer which most preferably is of a
27 semi-cylindrical shape. This transducer may be
28 provided with a backing of lead or other dense
29 material, and the backing may have a rear surface
30 shaped to minimise internal acoustic reflection.

31
32 Alternative transducer means include a capacitor-type
33 detector, which is preferably small and disk-shaped; an
34 integrated semiconductor pressure sensor; and an
35 optical pressure sensor, for example based on an
36 optical fibre.

1 In an alternative arrangement, the plane of the
2 transducer may be arranged to be perpendicular to the
3 optical axis to detect the acoustic wave which is
4 propagating in a direction opposite to the direction of
5 the light beam. For example, the acoustic transducer
6 means may be part-spherical with an aperture to allow
7 access for the light beam. This may be particularly
8 suitable for engagement with a body part other than the
9 finger, for example the back of the arm.

10
11 The generation of a surface acoustic wave is an
12 inherent aspect of the in vivo pulsed photoacoustic
13 generation in tissue and may be used to characterize
14 tissue properties such as density. A surface wave
15 detector may be provided in the sensing head assembly.

16
17 Preferably means are provided for ensuring a consistent
18 contact pressure between the selected body part and the
19 acoustic transducer means. In the case where the
20 selected part is the distal portion of the finger, said
21 means may be provided by mounting the portion of the
22 housing engaged by the finger in a resiliently biased
23 fashion against the remainder of the housing, and
24 providing means to ensure that measurement is effected
25 when the predetermined force or pressure is applied by
26 the subject against the resilient bias. In the case
27 where the selected part is the earlobe, said means may
28 be provided by placing the ear between two plates and
29 applying pressure to the ear with springs or weights or
30 other force method. The two plates holding the ear may
31 contain a removable insert. The two plates may be flat
32 or may be of another shape to optimally position the
33 detector with respect to the beam axis.

34
35 In addition, the present invention provides a sensor
36 head for use in photoacoustic in-vivo measurements,

1 comprising a housing shaped to receive a removable
2 insert, a removable insert that engages a selected body
3 part, the insert being fitted to an individual,
4 allowing for a range of sizes of body parts to be used,
5 and further comprising light transmission means
6 terminating in or near said removable insert so as to
7 transmit light energy from a light source or sources to
8 enter the body part along a beam axis, and an acoustic
9 transducer means mounted in the housing or in the
10 removable insert to receive acoustic waves generated by
11 photoacoustic interaction within the body part to
12 receive said acoustic waves in a direction of high
13 acoustic energy.

14
15 From another aspect the present invention provides an
16 in vivo measuring system comprising a sensor head as
17 hereinbefore defined in combination with a light source
18 coupled with the light transmission means, and signal
19 processing means connected to receive the output of the
20 acoustic transducer means and to derive therefrom a
21 measurement of a selected physiological parameter.

22
23 Preferably, the light transmission means is a fiber
24 distribution system where each light source is
25 connected to an individual fiber and when multiple
26 light sources are used the multiple fibres are joined
27 by some standard fiber combining method, such as a
28 wavelength division multiplexer or a fiber coupler.
29 The fiber that comes from the light source, or contains
30 the combined light for a multiple source system, is
31 then terminated in proximity to the body part being
32 measured. The fiber could be in contact with the body
33 part or alternatively standard optics, such as lenses,
34 beamsplitters and such, could be employed to convey the
35 light from the end of the fiber to the body part. A
36 reference detector or several reference detectors and

1 beamsplitters can be added to the optical distribution
2 system to determine the energy of the light entering
3 the body part.

4
5 Alternatively, the optical distribution system may
6 contain mechanical holders, lenses and such to convey
7 the light from the source, or sources, to a location in
8 proximity to the body part being measured. A reference
9 detector or several reference detectors and
10 beamsplitters can be added to the optical distribution
11 system to determine the energy of the light entering
12 the body part.

13
14 The acoustic signal from the detector contains
15 information in both time and frequency, and there may
16 be information from several sources. The processing
17 means is preferably a multi-dimensional processing
18 method, such as Classical Least Squares (CLS) or
19 Partial Least Squares (PLS). Alternatively the
20 processing method may be more flexible, such as a
21 Neural Network. In addition to these methods the
22 signals may be analysed for their frequency content
23 using such techniques as Fourier Analysis or Frequency
24 Filtering. In addition techniques may be employed that
25 use time information such as the time delay from source
26 trigger. Techniques that combine both frequency and
27 time information may be employed, such as Wavelet
28 analysis.

29
30 The light source is preferably a laser light source and
31 is most suitably a pulsed diode laser, but may utilise
32 a set of such lasers or utilise a tunable laser source.
33 In a particularly preferred form, suitable for use in
34 measuring blood glucose concentration, a laser diode is
35 used with a wave length in the range of approximately
36 600 nm to 10,000 nm and a pulse duration of the order

1 of 5 to 500 ns.

2

3 The delivery to the measurement site may be either
4 directly or by optical fibre with a suitable optical
5 element to focus the beam into the tissue.

6

7 Preferably means are provided for time multiplexing
8 multiple sources when multiple sources are used. Each
9 source is switched on, and it generates an optical
10 pulse, or a set of optical pulses. This pulse, or set
11 of pulses, generates an acoustic signal that is
12 detected by the detector. Each source is pulsed in
13 sequence until all sources have been used to generate
14 their own signal.

15

16 The measuring system may conveniently be in the form of
17 a self contained system including a power supply and a
18 readout, which may be carried on the person and used at
19 any convenient time.

20

21 It is also possible for such a self contained system to
22 incorporate, or to be provided with facilities for
23 connection to, a cellular telephone, two-way pager or
24 other communication device for routine transmission of
25 measurements taken to a central data collection point.

26

27 In addition the measuring system may have provision for
28 manipulating the body part under measurement and for
29 performing additional measurement of the tissue to get
30 other information about the state of the physiology of
31 the issue. It is well-known in the art that squeezing
32 a section of tissue to increase the pressure and then
33 releasing the pressure will cause changes in the total
34 blood volume in the measurement site. The present
35 invention may allow for this type of manipulation
36 including the squeezing of a body part, such as an

1 earlobe, and making photo acoustic measurements at
2 several different pressures. The present invention may
3 also allow for the measurement of the temperature of
4 the body site and to apply a correction to the
5 measurements based upon the temperature of the body
6 site.

7
8 Another type of physiological manipulation is body
9 temperature. It is known in the art that several
10 parameters involved in the detection of the photo
11 acoustic signal, such as the speed of sound, are
12 dependent upon the temperature of the medium the signal
13 is propagating through (the tissue). Also the
14 perfusion of the blood in the small capillaries is
15 dependent upon the temperature of the tissue.
16 Additional information about the tissue can be obtained
17 if the photo acoustic measurement is made at several
18 temperatures, both higher and lower than ambient
19 temperature. This additional information is used to
20 better eliminate interferences to the determination of
21 the analyte under investigation. These are only two
22 examples of manipulating the body site and are not
23 intended to be an exhaustive list, and they can be used
24 in combination with other manipulation techniques.

25
26 The in-vivo measuring system may comprise a means for
27 storing calibration coefficients or operation
28 parameters or both calibration coefficients and
29 operational parameters, in order to calibrate the
30 instrument and to set critical operational parameters.

31
32 Another aspect of the present invention provides a
33 means for adjusting the calibration coefficients and
34 operational parameters to be specific to a particular
35 person and may be used to adjust for such things as
36 body part size, skin color, skin condition, amount of

1 body fat, efficiency of the detector and efficiency of
2 the source(s).

3
4 In addition the present invention may provide for
5 having the specific calibration coefficients and
6 operational parameters be contained in a storage site
7 located in the removable insert. This allows for the
8 system to be both mechanically and operationally
9 configured to a particular individual. Additionally
10 the invention may allow for the calibration
11 coefficients and operational parameters to be stored in
12 two locations, one in the non-removable housing and one
13 in the removable insert with some of the coefficients
14 and parameters stored in each location. This allows
15 for reader system coefficients to be stored in the
16 reader and coefficients specific to an individual to be
17 stored in the removable insert for that person,
18 enabling many people to use the same reader.

19
20 Another aspect of the present invention provides means
21 for connecting the non-invasive measuring system to an
22 invasive measuring system for the purpose of
23 calibrating or adjusting the operational parameters of
24 the non-invasive measuring system. Such connection may
25 be accomplished, but is not limited to, communication
26 by a wire, IR link or radio waves.

27
28 Another aspect of the present invention provides a
29 method for removing instrument drift from the
30 measurement comprising the steps of:

- 31
- 32 1. Placing a standard in the reader in place of the
33 body part.
 - 34
 - 35 2. Measuring the signal from the standard for each
36 wavelength and storing the values in the

1 calibration storage location.

2

3 3. Before making a measurement of a body part,
4 placing the calibration standard in the reader.

5

6 4. Measuring the signal from the standard for each
7 source.

8

9 5. Comparing the just measured standard values to the
10 stored calibration values.

11

12 6. Calculating correction factors for each source
13 wavelength.

14

15 7. Removing the standard and placing the body part in
16 the reader.

17

18 8. Measuring the signal from the body part for each
19 source.

20

21 9. Adjusting the measured values using the calculated
22 correction factors.

23

24 In addition to the signal correction factors a
25 correction factor can be calculated for the instrument
26 temperature. This can be applied to each signal with a
27 different correction coefficient.

28

29 The invention further provides a method of measuring a
30 biological parameter in a subject, the method
31 comprising the steps of:

32

33 directing one or more pulses of optical energy
34 from the exterior into the tissue of a subject
35 along a beam axis, the optical energy having a
36 wavelength selected to be absorbed by tissue

1 components of interest, thereby to produce a
2 photoacoustic interaction;
3
4 detecting acoustic energy resulting from said
5 photoacoustic reaction by means of a transducer
6 positioned to intercept acoustic energy
7 propagating in a direction other than the forward
8 direction of said beam axis; and
9
10 deriving from said detected acoustic energy a
11 measure of the parameter of interest; and a
12 corresponding apparatus.
13
14

15 Embodiments of the invention will now be described, by
16 way of example only, with reference to the accompanying
17 drawings in which:-
18

19 Figs. 1A, 1B and 1C are side views illustrating the
20 principle of operation of one embodiment of the
21 present invention;
22

23 Fig. 2 is a schematic perspective view showing a
24 sensor head for use in carrying out the
25 measurement illustrated in Fig. 1;
26

27 Fig 3. is a cross section view of the sensor head
28 of Fig. 2;
29

30 Fig. 4 is a side view of the sensor head of Fig.
31 2;
32

33 Fig. 5 is a schematic perspective view of an
34 apparatus incorporating the sensor head of Figs. 2
35 to 4;
36

1 Fig. 6 is a perspective view illustrating an
2 alternative form of sensor head;

3
4 Fig. 7 is a schematic end view showing another
5 form of sensor head;

6
7 Figs. 8a and 8b are a cross-sectional side view
8 and a plan view, respectively, of a further sensor
9 head;

10
11 Fig. 9 is a cross-sectional side view of one more
12 embodiment of sensor head;

13
14 Fig. 10 is a perspective view of one type of ear
15 interface apparatus;

16
17 Fig. 11 is a schematic of a multiple laser optical
18 distribution system using lenses, mechanical
19 mounts and a reference detector;

20
21 Fig. 12 is a schematic of a multiple laser optical
22 distribution system using fiber optic cables and a
23 fiber Wavelength Division Multiplexer (WDM), a
24 beam splitter and a reference detector;

25
26 Fig. 13 is a perspective view of a finger
27 interface apparatus with removable inserts that
28 are moulded to fit one individual;

29
30 Fig. 13A shows part of the apparatus of Fig. 13 in
31 greater detail;

32
33 Fig. 14 is a schematic of a semi-spherical
34 detector that contains a hole for the light beam,
35 with a vacuum system and a fiber distribution
36 system;

Fig. 15 is a perspective view showing one form of the instrument utilizing the vacuum body interface, a semi-spherical detector and the multiple laser source with lenses and mechanical housing;

Fig. 16 is a perspective view showing one form of the instrument using an ear lobe body interface, with the added feature of being able to manipulate the pressure on the ear lobe; and

Figs. 17, 18 and 19 are graphs illustrating an example.

Referring to Fig 1, an important feature of the present invention lies in introducing light energy along an axis into an area of soft tissue and detecting the resulting acoustic response transverse to that axis. Accordingly, in the arrangement of Fig 1A light energy from a diode laser (not shown) is transmitted via a fibre-optic guide 10 to the tip of a finger 12. The photoacoustic interaction occurs in an approximately cylindrical region indicated at 14 from which acoustic energy is radiated in a generally cylindrical manner and is detected by a transversely arranged acoustic transducer 16.

In Figs 1B and 1C, the principle is similar. The finger 12 is pressed against a support with force F. In Fig 1B, the incident light beam indicated at L is directed as in Fig 1A, and the transducer 16 is at an angle of 45 degrees thereto. In Fig 1B, the angle is 90 degrees as in Fig 1A, but the incident beam is directed differently into the fingertip.

1 In the present embodiment, the laser wavelength is
2 chosen to achieve high degree of absorption by glucose
3 present in the blood. A suitable wavelength is in the
4 range approximately 1000 to 3000 nm. The laser pulse
5 duration is chosen to be short, typically of the order
6 of 5 to 500 ns, in order to minimise thermal diffusion
7 and thus to optimise the acoustic waveform. For the
8 same reasons, it is desirable to use a spot size which
9 is sufficiently small to minimise thermal diffusion,
10 typically a spot size of the order of 0.05 mm to
11 0.50 mm.

12
13 The efficiency of the photoacoustic detection is also
14 influenced by the positioning and dimensions of the
15 acoustic transducer in relation to the characteristic
16 extinction length of the tissue at the principal
17 wavelengths chosen for measurement. In the fingertip
18 arrangement of Fig. 1, the system efficiency will be
19 improved by optimising the length of the transducer
20 crystal parallel to the axis of the finger, but the
21 length should not be so great as to give rise to
22 undesired signals which would occur at the point of
23 entry of the optical energy into the finger and by
24 reason of interaction of the acoustic energy with bone
25 or other hard tissue.

26
27 A second limit on the size of the acoustic detector
28 derives from the wavelength of the acoustic wave in the
29 tissue. Again making use of Huyghens principal of
30 superposition we view each point of tissue, that is
31 illuminated by the incoming light, as a point source
32 that generates a spherical pressure wave. The signal
33 measured at the detector is just the superposition of
34 all pressure waves from all points that are illuminated
35 by the source light. Normally if the size of the
36 detector is increased then the signal should also

1 increase because more energy is received by the
2 detector. However if the acoustic detector is too
3 large then a pressure wave generated from a tissue
4 element will create a pressure wave that will strike
5 the both ends of the detector. If the paths length
6 from the tissue element to the first end of the
7 detector is different than the path length to the
8 second end of the detector and if this difference in
9 path length is about one half of the acoustic signal
10 wavelength then the signal will destructively interfere
11 with itself and will reduce the magnitude of the
12 measured signal.

13
14 Referring to Fig 2, one manner of carrying out the
15 arrangement shown in Fig 1 makes use of a sensor head
16 having a finger rest 18 which is slidably moveable
17 within housing 20 closed by a front plate 22. The user
18 inserts his finger in a semi-cylindrical depression 24
19 in the finger rest 18 with the finger tip engaged
20 against an end surface 28 which includes an exit face
21 26 of the optical fibre 10. The finger is then pressed
22 downwardly against a resilient bias to enable a
23 standardised contact to be obtained between the skin
24 and the acoustic transducer. The finger tip may first
25 be dipped in water or coated with an aqueous gel to
26 improve the acoustic coupling.

27
28 Referring to Figs 3 and 4, in this preferred
29 arrangement the acoustic transducer comprises a semi-
30 cylindrical piezoelectric transducer 30. The
31 transducer 30 is provided with a backing member 32 of
32 lead or another dense substance, the rear face 34 of
33 which is shaped in irregular curves. The use of the
34 semi-cylindrical transducer 30 maximises the area for
35 reception of acoustic energy from the finger, while the
36 use of a dense backing material minimises ringing

1 effects within the transducer. Additionally, the rear
2 face 34 is shaped as shown to reduce reflection of
3 acoustic energy back towards the piezo crystal.
4

5 Fig 3 also shows the finger rest biased upwardly by the
6 use of constant tension springs 38.
7

8 Fig 5 illustrates schematically the apparatus of Figs.
9 2 and 3 embodied in a self-contained, portable blood
10 monitoring apparatus including a user readout 40. An
11 apparatus of this nature allows a diabetic to monitor
12 blood glucose concentration in a convenient manner, as
13 frequently as may be desired, and in a painless and
14 discreet manner.
15

16 Other forms of photoacoustic sensor head are possible
17 within the scope of the present invention. For
18 example, Fig. 6 shows an arrangement in which a light
19 guide 50 and an acoustic transducer 52 are applied to a
20 finger 54 by means of a hinged clamp member 56. Fig. 7
21 shows a finger 60 engaged by a light guide 62 and an
22 acoustic transducer 64 which are carried on a moveable
23 assembly 66 with the finger 60 being trapped between
24 the moveable assembly 66 and a fixed anvil 68.
25

26 It is also possible to arrange the sensor head to co-
27 operate with a soft tissue surface of the body, for
28 example a soft part of the abdomen. Figs. 8a and 8b
29 show an arrangement in which a cup shaped member 70,
30 suitably of rubber, causes a light guide 72 and an
31 acoustic transducer 74 to be contacted with a bulge of
32 soft tissue 76 which may for example be drawn into
33 contact by means of a partial vacuum within the member
34 70 caused by suction through a conduit 78, or by other
35 mechanical or adhesive means.
36

1 A somewhat similar arrangement is shown in Fig. 9 in
2 which a planar mount 80 carrying a light guide 82 and
3 acoustic transducer 84 is secured to a soft area of
4 body by means of surgical adhesive 86.

5
6 Referring to Fig. 10, one method of performing
7 measurement on an ear lobe involves placing the ear
8 lobe between a fixed plate 87 and a movable plate 88.
9 The acoustic detector 89 is mounted partially
10 perpendicular that is at an acute angle, to the beam
11 axis defined as line going from the center of a lens 90
12 to the center of a window 91. It has been found that
13 the system works satisfactorily with the detector 89 at
14 an angle of 45° to the beam axis. The window 91 and
15 the detector 89 are placed in direct contact with the
16 ear and the opposite plate 88 places pressure on the
17 ear using a suitable mechanism (not shown). This
18 particular embodiment of the ear interface apparatus
19 incorporates an alignment ring 92 which is temporarily
20 attached to the ear and fits over the window housing 91
21 to aid in aligning ear into the same location every
22 time.

23
24 Referring to Fig. 11, one method of combining light
25 sources into the instrument is to use a mechanical
26 housing 93 with several holes used to align lenses 95
27 and laser diodes 94. The housing shown uses a
28 hexagonal array of seven holes. The sources and lenses
29 are arranged in such a way that they all focus to the
30 same location 96 which could be on the surface of the
31 body part. This design does not show the inclusion of
32 beamsplitters and reference detectors but they can be
33 added in an alternative arrangement.

34
35 An alternative method of combining several sources into
36 one beam is shown in Fig. 12. Several laser diodes 97

1 are shown coupled to individual fiber optic cables 131.
2 These cables 132 are combined using a fiber Wavelength
3 Division Multiplexer (WDM) 98. Alternative combination
4 methods exist including couplers and multi-fiber
5 bundles. The combined light exits the WDM 98 in a
6 single fiber 104 and terminates at the focal point of a
7 lens 131. This end of the fiber is imaged to the end
8 of the finger 103 to a spot 102 using another lens 130.
9 Some of the light is split off the main beam using a
10 beam splitter 100 and focused onto a reference detector
11 101 using another lens 99. Additional reference
12 detectors and/or beamsplitters can be added to the
13 distribution system without changing its function.
14 Alternatively a reference detector could look directly
15 at the body part to measure the light reflecting off
16 the surface, as a measure of the overall light energy
17 entering the body part.

18
19 Referring to Fig. 13, another method of using a finger
20 as the body part and including removable inserts is
21 shown. A finger 105 is inserted into an insert 106
22 that is used to customize the finger holder to a
23 particular finger. The moulded insert 106 is placed
24 into a housing 107. The finger 105 is placed against a
25 semi-cylindrical acoustic detector in a module 108 which
26 is also attached to the housing 107. A cover 109 for
27 the housing 107 contains a mechanism 111 to apply
28 constant force to the finger 105. The light beam 110
29 is introduced into the finger 105 using a suitable
30 optical distribution system (not shown). Fig. 13A shows
31 the module 108 in greater detail. A base 200 carries a
32 part-cylindrical piezo transducer 202 on a support 204.
33 206 indicates a coaxial connector to communicate the
34 transducer signal.

35

36 Fig. 14 shows a schematic of an alternative to the

1 vacuum arrangement shown in Figs. 8 and 9. In this
2 system a photoacoustic reader 121 is placed against the
3 skin 113 with a semi-spherical detector 112 in contact
4 with the skin 113. A vacuum pump 115 and vacuum seal
5 116 create a negative pressure and pull the skin 113
6 against the detector 112. Processing electronics 119
7 energizes light sources 118 and an optical distribution
8 system 117 routes the light to the body part through a
9 hole in the top of the semi-spherical detector 112.
10 The optical distribution system 117 directs a small
11 portion of the light to a reference detector 114. The
12 processing electronics 119 measures the signal from the
13 acoustic detector 112 and the reference detector 114
14 for each optical source 119 and calculates the glucose
15 value. The value is displayed on a display 120.

16
17 Fig. 15 shows a similar system 125, only using another
18 type of optical distribution system 127. Again a
19 vacuum pump 123 creates a negative pressure which draws
20 the skin up to an acoustic detector 122. Processing
21 electronics 124 signals light sources in optical
22 distribution system 127 to illuminate and a signal is
23 generated at acoustic detector 122. The processing
24 electronics 124 calculates the proper value and
25 displays it on a display 126.

26
27 Fig. 16 shows an alternative arrangement of a photo-
28 acoustic reader. In this system 128, the vacuum system
29 is replaced with an ear squeeze mechanism 129 which
30 applies pressure to the ear. An acoustic detector 130
31 detects the signals from the ear lobe.

32
33 In the most straightforward forms of the invention, a
34 single analyte such as glucose in blood can be measured
35 by using light of selected wavelengths and by measuring
36 the area or the amplitude of the received acoustic

pulse. It is preferable to make each measurement by using a train of pulses, for example about 100 pulses, and averaging the results in order to minimise the effects of noise and pulse effects in the blood flow.

The accuracy of the detection system is governed, in part, by the Signal to Noise Ratio (SNR) of the system. Variations in the intensity and duration of the light source can cause the acoustic signal to contain variations. A normalization technique, such as taking the ratio of the acoustic signal to the optical signal, can significantly reduce the effect of the source variations, thereby improving the signal to noise ratio of the system. The optical signal can be measured with a reference detector, or several reference detectors, one for each source or one for a wavelength range. An equation describing this type of normalization follows:

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{\text{Optical Signal}}$$

In some cases the relationship between the optical signal and the acoustic signal changes with wavelength and light intensity. When this is the case the accuracy of the measurement can be further enhanced by determining the energy dependence of the photoacoustic signal. This may be determined by establishing the specific relationship between the photoacoustic signal and the incident energy from a set of measurements and using this relationship to compensate for the non linear response. An equation describing this type of normalization is as follows:

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{\text{Incident Energy}}$$

Scaling Factor *Optical Signal +
Offset

Other normalization methods can also apply. The time interval between the optical pulse and the detection of the acoustic signal may be used to characterise physical properties such as the velocity of sound in the tissue. In addition, in another embodiment of the device the damping of the acoustic oscillations may be used to monitor the elastic properties of the tissue and, in particular, the compressibility. Both of these aspects may be used in the person to person calibration of the photoacoustic response.

More complex analysis of the received acoustic energy is possible. For example, a time-gating technique may be used to derive measurement at varying depths within the tissue being examined. Alternatively, an array of detectors can be employed to determine the profile of the absorption of the acoustic signal at different depths and locations. This depth profile will change with the absorption coefficient and could be used as additional information to determine the analyte concentration. It is also possible to derive information relating to a number of analytes of interest by more sophisticated analysis of the received acoustic energy wave forms, for example by analysis of the frequency spectrum by Fourier transform or wavelet analysis techniques.

Alternatively, or in combination with the frequency techniques and multiple detectors, multiple light sources can aid in the determination of the concentration of a number of analytes.

There are a number of tissue features which may vary

1 from person to person or with in the same person over
2 time which impact the photoacoustic signal observed.
3 To obtain an accurate measurement of a given analyte,
4 such as glucose, it may be helpful to also determine
5 the concentration of other analytes such as haemoglobin
6 which may act as interferants. One approach is to
7 generate several distinct photoacoustic signals using
8 excitation light of several different wavelengths. For
9 example, excitation light of a wavelength of which
10 haemoglobin absorbs strongly but glucose has little if
11 any absorption could be used to obtain a measure of the
12 haemoglobin concentration with which to normalize the
13 effect of haemoglobin on measurements made on different
14 persons or on the same person at different times.
15 These measurements which are to be normalized might be
16 based on the photoacoustic signal generated by light of
17 a wavelength at which glucose absorbs.

18
19 It is also possible to measure the concentration of
20 such interferants by other means, such as infrared
21 light absorption, and thus normalize or correct the
22 photoacoustic signal representative of the desired
23 analyte for variations in these interferants. Thus,
24 for example, the photoacoustic signal representative of
25 glucose could be corrected for variations in
26 haemoglobin concentration determined by optical
27 absorption techniques such as those taught in US Patent
28 No 5,702,284.

29
30 For the reliable and reproducible determination of
31 glucose a signal to noise ratio of at least 10,000 is
32 recommended. In this regard water is typically present
33 in human tissue of a concentration of about 50 molar
34 while glucose is present at a concentration of about 5
35 millimolar in a normal individual.

36

1 Apparatus and method embodying the present invention
2 have been found to yield accurate and repeatable
3 results. In the case of blood glucose measurement, the
4 clinical range of glucose concentration is
5 approximately 5-10 m mol/l in healthy subjects, and up
6 to 40 m mol/l in diabetics. An analysis based on
7 simple absorption models suggests that the change in
8 photoacoustic signal over this range might be as little
9 as 0.2%. The present invention has been found to
10 provide a change in photoacoustic signal of up to 140%
11 for a change in glucose concentration of 15m mol/l.

12
13 The precise mechanisms involved are not at present
14 fully understood. It is believed, however, that
15 absorption occurs primarily in body plasma and is
16 modified by the presence of glucose, and that this
17 affects beam geometry.

18
19 Example

20
21 The blood glucose levels of three individuals, one
22 normal individual, one type 1 diabetic and one type 2
23 diabetic, were followed over a two hour period
24 following each individual taking about 75 grams of
25 glucose orally in an aqueous solution by both
26 photoacoustics and direct blood measurement. The
27 results are reported in Figures 17, 18 and 19.
28 Photoacoustic measurements were made every five minutes
29 and blood measurements were made every ten minutes. The
30 blood samples were venous blood samples analysed by the
31 standard glucose oxidase method using a Yellow Springs
32 instrument. The error bands for the blood measurements
33 were derived from the literature accompanying the
34 testing instrument while those for the photoacoustic
35 results were based on the averages taken over 1000
36 pulses. The results were obtained from a configuration

1 similar to that illustrated in Figure 1 in which 10 was
2 an end of a 1 km multimode fibre optic cable which was
3 placed against the finger 12. The other end received
4 600 nanosecond pulses of 1040 nanometer light from a Q
5 switched Nd:YAG laser delivering 2,7 micro joules per
6 pulse for each measurement. Raman interactions in the
7 fibre caused the production of light an additional
8 wavelengths as set forth in the following table:

9
10
11
12

Wavelength in nm	Average pulse energy in microJoules	Pulse width in ns	Approximate bandwidth in nm
1064	2.7	600	4
1120	2.25	500	6
1176	2.0	450	8
1240	1.5	425	12
1308	0.85	400	15
1390	0.3	350	20
1450	0.1	350	20
1500	0.2	350	20
1550	0.18	360	20

13
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32

33 The resulting photoacoustic signal was detected by a
34 5mm disc transducer with a lead backing and fed to an
35 amplifier and an oscilloscope. The transducer was
36 generally placed as 16 in Figure 1 but was not

1 precisely parallel to the beam axis; its detection
2 plane was at an angle of about 20 degrees to the beam
3 axis. The photoacoustic signal was evaluated in terms
4 of the difference in voltage signal from the positive
5 peak of the compression to the negative peak of the
6 relaxation of the acoustic pulse.

7

8 The change in photoacoustic response correlated well
9 with the change in blood glucose concentration over the
10 two hour measurement period. A correlation of 0.89 was
11 achieved on samples ranging from 4 to 35 m mol/l.

12

13 Other modifications and improvements may be made to the
14 foregoing embodiments within the scope of the present
15 invention as defined in the claims.

16

1 CLAIMS

- 2
- 3 1. A sensor head for use in photoacoustic in vivo
4 measurement, comprising a housing shaped to engage
5 a selected body part, light transmission means
6 terminating in said housing so as to transmit
7 light energy from a light source to enter the body
8 part along a beam axis, and acoustic transducer
9 means mounted in the housing to receive acoustic
10 waves generated by photoacoustic interaction
11 within the body part, the acoustic transducer
12 means being disposed in the housing to receive
13 said acoustic wave in a direction of high acoustic
14 energy.
15
- 16 2. A sensor head according to claim 1, in which the
17 acoustic transducer means is arranged at least
18 partially perpendicular to the optical beam axis.
19
20
- 21 3. A sensor head according to claim 2, for use where
22 the selected body part is the distal portion of a
23 finger, in which the housing includes a generally
24 half-cylindrical depression in which the finger
25 may be placed with the light transmission means
26 aimed at the end of the finger.
27
- 28 4. A sensor head according to any preceding claim, in
29 which the acoustic transducer means comprises a
30 piezoelectric transducer which is of a semi-
31 cylindrical shape.
32
- 33 5. A sensor head according to any preceding claim, in
34 which the acoustic transducer means comprises a
35 piezoelectric transducer which is provided with a
36 backing of lead or other dense material.

- 1 6. A sensor head according to claim 5, in which said
2 backing has a rear surface shaped to minimise
3 internal acoustic reflection.
4
- 5 7. A sensor head according to any of claims 1 to 4,
6 in which the transducer means comprises a
7 capacitor-type detector.
8
- 9 8. A sensor head according to any of claims 1 to 4,
10 in which the transducer means comprises a
11 piezoelectric transducer arranged generally
12 perpendicular to the optical axis to detect the
13 acoustic wave which is propagating in a direction
14 opposite to the direction of propagation of the
15 light beam.
16
- 17 9. A sensor head according to claim 8, in which the
18 transducer is part-spherical with an aperture to
19 allow access for the light beam.
20
- 21 10. A sensor head according to any preceding claim,
22 including a surface wave detector for
23 characterizing tissue properties.
24
- 25 11. A sensor head according to any preceding claim,
26 including means for ensuring a consistent contact
27 pressure between a selected body part and the
28 acoustic transducer means.
29
- 30 12. A sensor head according to claim 11, for use where
31 the selected part is the distal portion of a
32 finger, said means being provided by mounting a
33 portion of the housing engaged by the finger in a
34 resiliently biased fashion against the remainder
35 of the housing, and providing means to ensure that
36 measurement is effected when a predetermined force

1 or pressure is applied by the subject against the
2 resilient bias.

3

4 13. A sensor head according to claim 11, for use where
5 the selected part is the earlobe, said means being
6 provided by two plates, between which the earlobe
7 may be placed, and means for pressing the plates
8 together to apply pressure to the ear.

9

10 14. A sensor head for use in photoacoustic in-vivo
11 measurements, comprising a housing shaped to
12 receive a removable insert; a removable insert
13 that engages a selected body part, the insert
14 being fitted to an individual, allowing for a
15 range of sizes of body parts to be used; light
16 transmission means terminating in or near said
17 removable insert so as to transmit light energy
18 from a light source to enter the body part along a
19 beam axis; and an acoustic transducer means
20 mounted in the housing or in the removable insert
21 to receive acoustic waves generated by
22 photoacoustic interaction within the body part,
23 the acoustic transducer means being disposed in
24 the housing or insert to receive said acoustic
25 waves in a direction of high acoustic energy.

26

27 15. An in vivo measuring system comprising in
28 combination: a sensor head as claimed in any
29 preceding claim; a light source coupled with the
30 light transmission means; and signal processing
31 means connected to receive the output of the
32 acoustic transducer means and to derive therefrom
33 a measurement of a selected physiological
34 parameter.

35

36 16. The system of claim 15, in which the light

1 transmission means is a fiber optic distribution
2 system.

3

4 17. The system of claim 16, in which there is a
5 plurality of light sources each connected to an
6 individual fiber and the respective fibers are
7 joined by a wavelength division multiplexer or a
8 fiber coupler.

9

10 18. The system of claim 16 or claim 17, in which the
11 fiber optic distribution system terminates in
12 contact with the body part.

13

14 19. The system of claim 16 or claim 17, in which the
15 fiber optic distribution system communicates with
16 the body part via optical elements such as lenses
17 and beamsplitters.

18

19 20. The system of claim 15, in which the light
20 transmission means comprises optical elements
21 mounted in mechanical holders and arranged to
22 convey the light from the light source to a
23 location in proximity to the body part.

24

25 21. The system of claim 19 or claim 20, in which the
26 light transmission means includes at least one
27 beamsplitter arranged in the light path to direct
28 a portion of the light to a respective reference
29 detector to measure the energy of the light
30 entering the body part.

31

32 22. The system of any of claims 15 to 21, in which the
33 signal processing means is adapted to perform a
34 multi-dimensional processing method.

35

36 23. The system of claim 22, in which the signal

1 processing means is adapted to perform one of
2 Classical Least Squares or Partial Least Squares.
3
4

5 24. The system of any of claims 15 to 21, in which the
6 signal processing means comprises a Neural
7 Network.
8
9

10 25. The system of any of claims 15 to 24, in which the
11 signal processing means is operable to analyse the
12 signals for their frequency content using one of
13 Fourier Analysis and Frequency Filtering.
14

15 26. The system of any of claims 15 to 25, in which the
16 signal processing means additionally applies
17 techniques that use time information.
18

19 27. The system of claim 26, in which the time
20 information processed is the time delay from
21 source trigger.
22

23 28. The system of any of claims 15 to 25, in which the
24 signal processing means additionally applies
25 techniques that combine both frequency and time
26 information.
27

28 29 The system of claim 28, in which the signal
29 processing means performs wavelet analysis.
30

31 30. The system of any of claims 15 to 29, in which the
32 light source is a laser light source.
33

34 31. The system of claim 30, in which said laser light
35 source is selected from a pulsed diode laser, a
36 set of pulsed diode lasers, and a tunable laser

1 source.

2

3 32. The system of claim 31, for use in measuring blood
4 glucose concentration, in which the light source
5 is a laser diode with a wavelength in the range of
6 approximately 600 nm to 10,000 nm and a pulse
7 duration of the order of 5 to 500 ns.

8

9 33. The system of any of claims 30 to 32, in which the
10 light transmission means is arranged to produce a
11 spot size of the order of 0.05 mm to 0.50 mm.

12

13 34. The system of any of claims 15 to 29, in which
14 there are multiple light sources and means are
15 provided for time multiplexing the multiple
16 sources such that: each source is switched on and
17 generates an optical pulse, or a set of optical
18 pulses, the pulse, or set of pulses, generates an
19 acoustic signal that is detected by the detector,
20 and each source is pulsed in sequence until all
21 sources have been used to generate their own
22 signals.

23

24 35. The measuring system of any of claims 15 to 34, in
25 the form of a self contained system including a
26 power supply and a readout, which may be carried
27 on the person and used at any convenient time.

28

29 36. The system of claim 35, including facilities for
30 connection to a cellular telephone, two-way pager
31 or other communication device for routine
32 transmission of measurements taken to a central
33 data collection point.

34

35 37. The system of any of claims 15 to 36, further
36 including means for manipulating the body part

1 under measurement and for performing additional
2 measurement of the tissue to obtain other
3 information about the state of the physiology of
4 the issue.

5
6 38. The system of claim 37, in which said manipulating
7 means includes means for squeezing a body part,
8 such as an earlobe, and means for making photo
9 acoustic measurements at several different
10 pressures.

11
12 39. The system of claim 37 or claim 36, including
13 temperature measurement means for measuring the
14 temperature of the body site, and in which the
15 signal processing means is arranged to apply a
16 correction to the measurements based upon the
17 temperature of the body site.

18
19 40. The system of claim 39, further including means
20 for inducing temperatures above and below ambient
21 in the body part.

22
23 41. The system of any of claims 15 to 40, comprising a
24 means for storing one or both of calibration
25 coefficients and operational parameters in order
26 to calibrate the instrument and to set critical
27 operational parameters.

28
29 42. The system of claim 41, in which the signal
30 processing means is operable to adjust the
31 calibration coefficients and operational
32 parameters to be specific to a particular person.

33
34 43. The system of claim 42, when dependent upon claim
35 14, in which the calibration coefficients and
36 operational parameters specific to a particular

1 person are contained in a storage site located in
2 the removable insert.

3

4 44. The system of claim 43, in which additionally
5 calibration coefficients and operational
6 parameters specific to the reader system are
7 stored in the non-removable housing.

8

9 45. The measuring system of any of claims 15 to 44,
10 further including connection means for connecting
11 the measuring system to an invasive measuring
12 system for the purpose of calibrating or adjusting
13 the operational parameters of the non-invasive
14 measuring system.

15

16 46. The system of claim 45, in which the connection
17 means is selected from a cable link, IR link or
18 radio waves.

19

20 47. A method of operating a measurement system as
21 claimed in claim 34 to remove instrument drift
22 from the measurement, the method comprising the
23 steps of:

24

25 1) placing a calibration standard in the reader
26 in place of the body part;

27

28 2) measuring the signal from the standard for
29 each wavelength and storing the values in the
30 calibration storage location;

31

32 3) before making a measurement of a body part,
33 placing the calibration standard in the
34 reader;

35

36 4) measuring the signal from the standard for

- 1 each source;
- 2
- 3 5) comparing the just measured standard values
- 4 to the stored calibration values;
- 5
- 6 6) calculating correction factors for each
- 7 source wavelength.
- 8
- 9 7) removing the standard and placing the body
- 10 part in the reader;
- 11
- 12 8) measuring the signal from the body part for
- 13 each source; and
- 14
- 15 9) adjusting the measured values using the
- 16 calculated correction factors.
- 17
- 18 48. The method of claim 47, in which a further
- 19 correction factor is calculated for the instrument
- 20 temperature.
- 21
- 22 49 A method of measuring a biological parameter in a
- 23 subject, the method comprising the steps of:
- 24
- 25 directing one or more pulses of optical
- 26 energy from the exterior into the tissue of a
- 27 subject along a beam axis, the optical energy
- 28 having a wavelength selected to be absorbed
- 29 by tissue components of interest, thereby to
- 30 produce a photoacoustic interaction;
- 31
- 32 detecting acoustic energy resulting from said
- 33 photoacoustic reaction by means of a
- 34 transducer positioned to intercept acoustic
- 35 energy propagating in a direction other than
- 36 the forward direction of said beam axis; and

deriving from said detected acoustic energy a measure of the parameter of interest.

50 The method of claim 49, in which the parameter of interest is blood glucose, and the optical energy has a wavelength in the range of approximately 600 nm to 10,000 nm and a pulse duration of the order of 5 to 500 ms.

51 The method of claim 49 or claim 50, in which a train of pulses is applied and the detected signals are averaged to derive said measure.

52 The method of any of claims 49 to 51, in which said measure is derived from the energy of the detected signal.

53 The method of any of claims 49 to 52, in which the optical energy is directed into a body part which is substantially composed of soft tissue and free of bone.

54 Apparatus for measuring a biological parameter in a subject, the apparatus comprising:

means for directing one or more pulses of optical energy from the exterior into the tissue of a subject along a beam axis, the optical energy having a wavelength selected to be absorbed by tissue components of interest, thereby to produce a photoacoustic interaction;

transducer means arranged to detect acoustic energy resulting from said photoacoustic reaction by intercepting acoustic energy propagating in a direction other than the forward direction of said



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Claims searched: 1 to 55

Examiner: Grant Bedford
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Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): G1G (GPB)

Int Cl (Ed.6): G01N (21/17 33/483 33/487 33/49), A61B (5/00 5/14)

Other: Online: WPI INSPEC

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	EP 0282234 A1 (DOWLING) See figure 4 and page 8 lines 1 to 3 in particular.	1 and 14 at least
X,E	EP 0829224 A2 (COLUMBUS) See figure 2 in particular.	1 and 14 at least
X,E	EP 0829225 A2 (COLUMBUS) See figure 1 in particular.	1 and 14 at least
X	Medical & Biological Engineering & Computing, Vol. 31(3), pp. 284-290, May 1993	1 and 14 at least
X	Physics in medicine and biology, Vol. 38(12), pp. 1911-1922, Dec 1993	1 and 14 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

- 1 60 The method of claim 59 in which the analyte is
2 glucose.
3
4 61 A method of normalizing a photoacoustic signal
5 obtained from directing an optical beam on the
6 tissue of a living being comprising determining
7 the dependence of the photoacoustic signal on the
8 energy of the optical beam from a series of
9 measurements at different energies for the type of
10 tissue involved.
11
12
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